

Preparing Electronic Drug Establishment Registration and Drug Listing Submissions in SPL Format

SPL R4 Training Face-to-Face Training Session –
May 21, 2009

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Agenda

| | |
|----------------------|--|
| 9:30 am - 9:35 am | Welcome |
| 9:35 am - 10:00 a.m. | DUNS Number Presentation & Q&A Session – Ryan Paul – D&B |
| 10:00 am - 10:15 am | SPL Overview & NDC Labeler Code SPL Documents |
| 10:15 am - 10:30 am | Break |
| 10:30 am - 11:30 am | Establishment Registration SPL Documents (Domestic & Foreign – Importers and US Agents) |
| 11:30 am - 12:45 pm | Lunch |
| 12:45 pm - 2:15 pm | Listing & Content of Labeling SPL Documents Combination Products, Listing Active Pharmaceutical Ingredients Listing Repackaged/Relabeled Drug Products |
| 2:15 pm - 2:45 pm | Data Relationships, Gateway Submissions SPL R4 Submission Feedback from FDA (Error messages) |
| 2:45 p.m. – 3:00 | Pillbox – SPL Product Images – David Hale, NLM |
| 3:00 pm - 3:30 pm | Q&A Session – Moderator - Virginia Hogan, Teva |
| 3:30 pm | End Training Session |

Taking Training Notes?

- PDF version of presentation slides will be e-mailed to attendees after training.

DUNS Numbers Presentation

Structured Product Labeling Overview

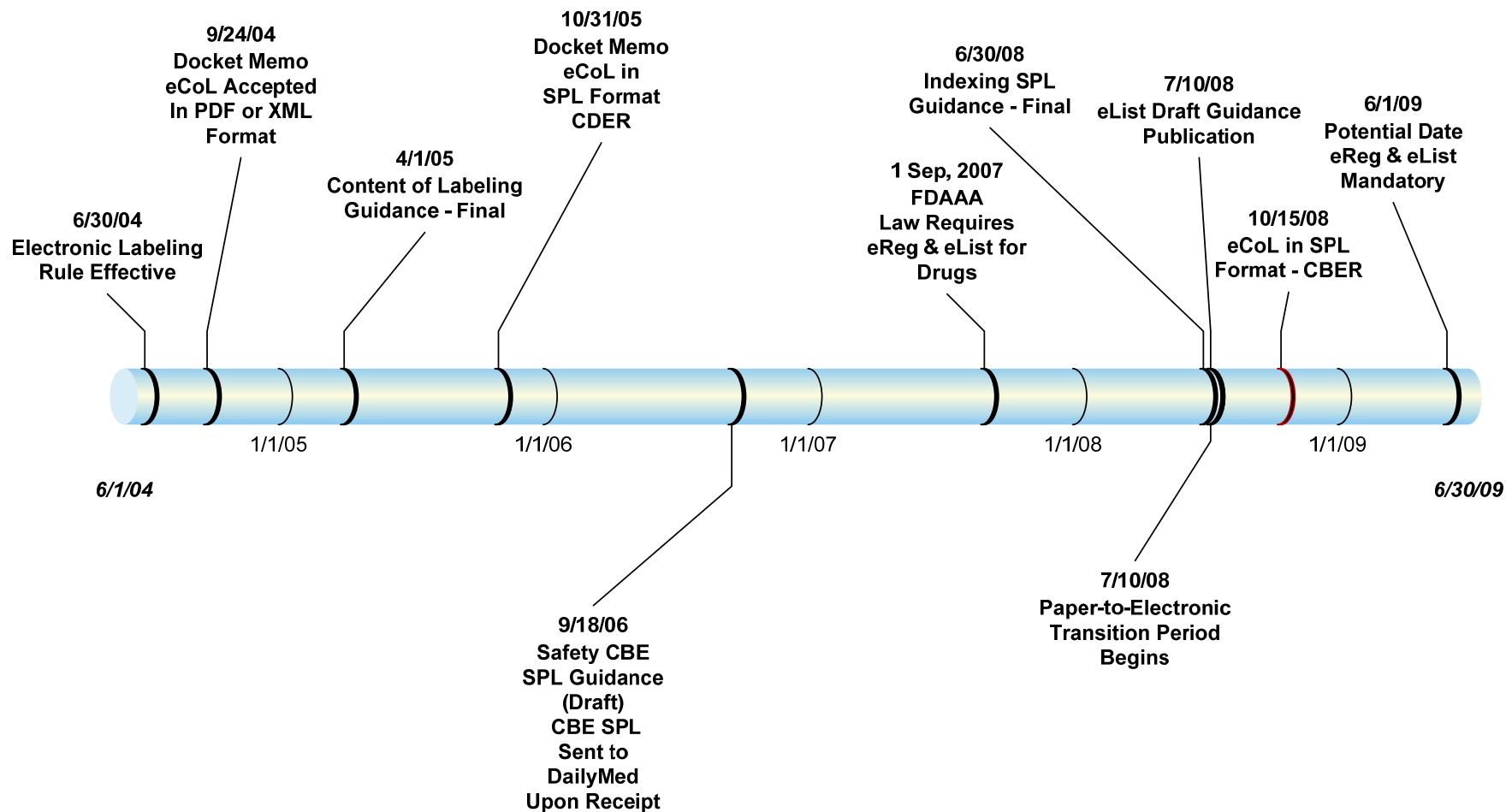
SPL Standard

- The Structured Product Labeling (SPL) is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product information.
- American National Standards Institute (ANSI) accredited (SPL Release 4) – March 2009
- SPL is created using **EX**tensible **M**arkup **L**anguage

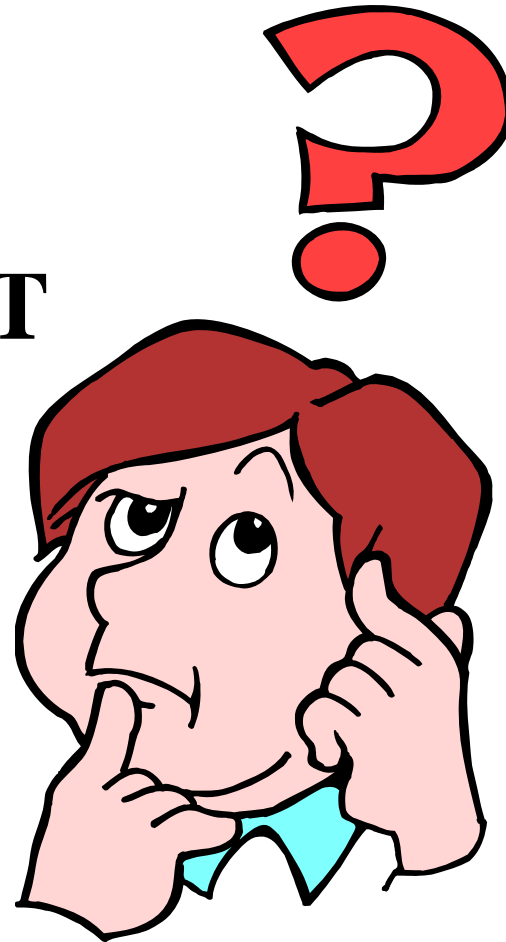
XML & XSL Stylesheet

- XML – **EX**tensible **M**arkup **L**anguage
 - Relatively human-legible
 - Machine readable
 - Tags (elements) permit search of key information
- XML Documents – created via Notepad, Word Pad, XML validation tools, Xforms, etc...
- XSL Stylesheet – transforms the XML data to be viewed via web browser or printed documents

IMPLEMENTATION OF STRUCTURED PRODUCT LABELING AT FDA



**WHY CHANGE
THE DRUG LISTING
AND ESTABLISHMENT
REGISTRATION
PROCESS THAT HAS
WORKED FOR
DECADES ????**



This is a screenshot of the FDA Form 2091 (a), which is used for submitting a New Drug Application (NDA). The form is divided into several sections, including:

- Section 1: Drug Information** - Contains fields for drug name, manufacturer, and other identifying information.
- Section 2: Manufacturing Information** - Includes details about the manufacturing process, facilities, and quality control.
- Section 3: Regulatory Information** - Contains information about the drug's regulatory status, including whether it is a new drug, a combination product, or a biologics license application (BLA).
- Section 4: Clinical Data** - Includes information about clinical trials, including the number of subjects, the results of the trials, and the safety of the drug.
- Section 5: Other Information** - Includes information about the drug's marketing, distribution, and other relevant details.

This is a screenshot of the FDA Form 2091 (b), which is used for submitting a New Drug Application (NDA). The form is divided into several sections, including:

- Section 1: Drug Information** - Contains fields for drug name, manufacturer, and other identifying information.
- Section 2: Manufacturing Information** - Includes details about the manufacturing process, facilities, and quality control.
- Section 3: Regulatory Information** - Contains information about the drug's regulatory status, including whether it is a new drug, a combination product, or a biologics license application (BLA).
- Section 4: Clinical Data** - Includes information about clinical trials, including the number of subjects, the results of the trials, and the safety of the drug.
- Section 5: Other Information** - Includes information about the drug's marketing, distribution, and other relevant details.

This is a screenshot of the FDA Form 2091 (c), which is used for submitting a New Drug Application (NDA). The form is divided into several sections, including:

- Section 1: Drug Information** - Contains fields for drug name, manufacturer, and other identifying information.
- Section 2: Manufacturing Information** - Includes details about the manufacturing process, facilities, and quality control.
- Section 3: Regulatory Information** - Contains information about the drug's regulatory status, including whether it is a new drug, a combination product, or a biologics license application (BLA).
- Section 4: Clinical Data** - Includes information about clinical trials, including the number of subjects, the results of the trials, and the safety of the drug.
- Section 5: Other Information** - Includes information about the drug's marketing, distribution, and other relevant details.

- Eliminate duplicative and redundant data entry
- Eliminate paper submissions
- Automate processing of data in a submission type in electronic format in a manner that FDA can adequately process, review, and archive.

Transition from Paper to Electronic Drug Establishment Registration & Drug Listing

- Changes in FD&C Act require electronic registration of drug establishments and listing of human prescription drugs, OTC, animal drug, biologic products – September 2007
- Draft Guidance document for electronic drug establishment registration and listing – July 2008
- FDA is adopting the use of extensible markup language (XML) files in SPL format as the standard format for the exchange of drug establishment registration and drug listing information.

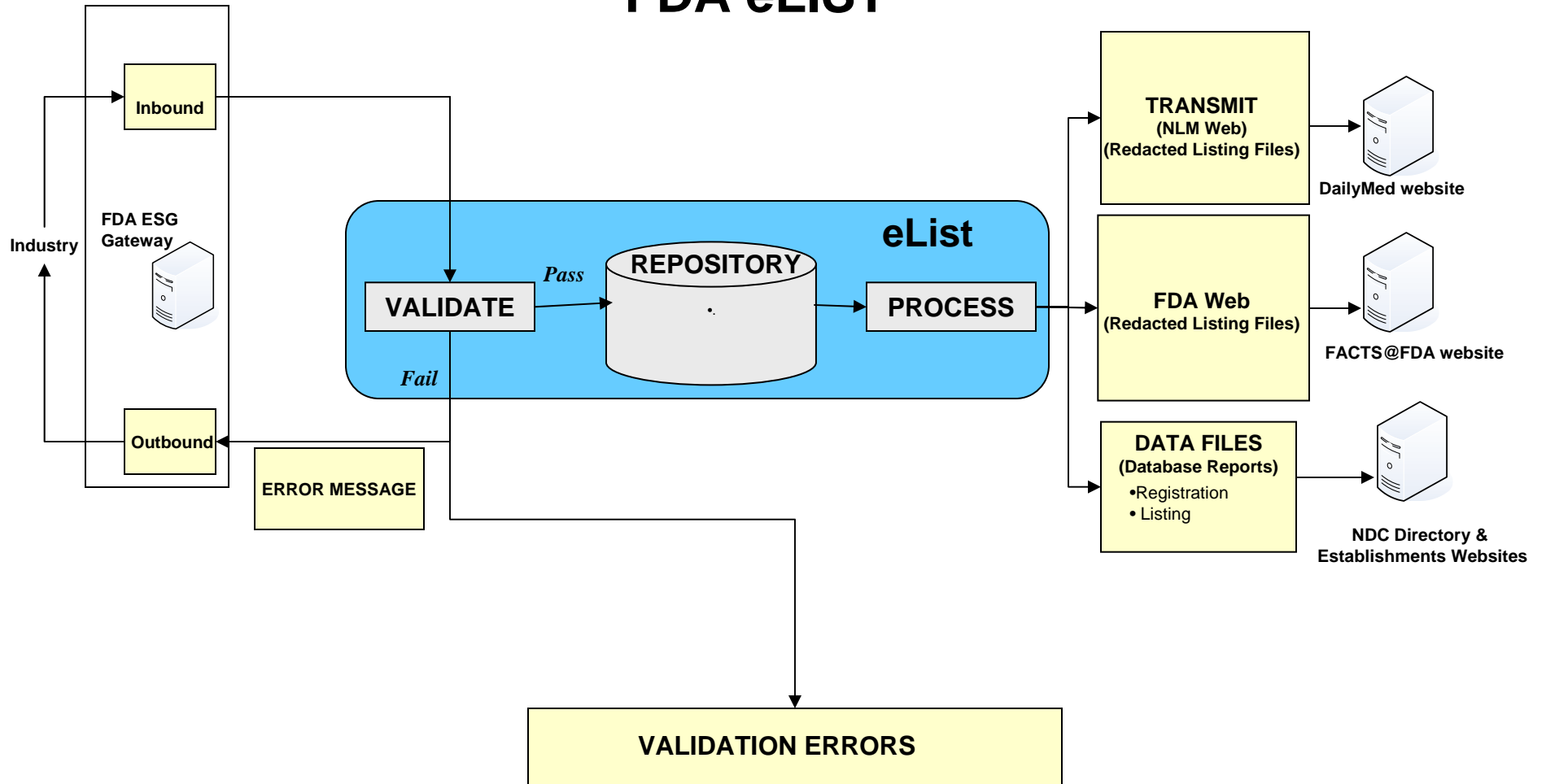
Benefits of Electronic Registration and Listing

- Electronic registration and listing process is more efficient and effective for industry and the Agency
- Accurate, up-to-date inventory of marketed drugs
- Eliminates data entry errors
- Eliminates the use of paper forms for listing and registration
- 24-hour submission window – FDA Gateway
- Reduces the amount of time for FDA to receive and process your information.
- Well formed and properly created SPL files can be processed in minutes
- Receive submission feedback in timely manner
- OTC drug product listing data is included in database

Transitioning from Paper to Electronic: Drug Registration and Listing

- If you electronically list your product(s) do not list the same product(s) using paper (FDA Form 2657 or FDA Form 2658)
- If you register your drug establishment(s) electronically, do not register the same drug establishment(s) using the paper (FDA Form 2656)

FDA eLIST



NDC Labeler Code SPL

NDC Labeler Codes

- Labeler code already assigned?
 - Submit labeler code SPL file to add your labeler code to our electronic system
 - Submit only labeler codes to be utilized in NDCs which will be included in future drug listing SPL documents (match labeler code

NDC Labeler Codes

- Request for new labeler code
 - Only if you need a new labeler code to generate NDCs to distribute products
 - Do not request labeler code just to register a new drug establishment
 - Current paper-based processing labeler code drug establishment relationship non-existent in eList

Registering Drug Establishments in SPL Format

Registering Drug Establishments in SPL Format

- Each Registrant (owner/operator firm) must submit one SPL file with registration information for all of its facilities (unlimited amount of domestic or foreign establishments permitted per file)
- Subsidiaries can be considered as registrants in ER SPL files

Establishment Registration SPL Document

| Product Information | |
|---------------------|----------------------------|
| Product Type | ESTABLISHMENT REGISTRATION |

| Registrant - Acme, Inc. (2223334441) | | | |
|--------------------------------------|--|------------------|------------------------|
| Contact | Address | Telephone Number | Email Address |
| Deborah Tyler | Address: 222 Bonifant Avenue City, State, Zip: Fort Washington, PA, 35295 Country: USA | +1-800-435-4585 | deborah.tyler@acme.com |

| Establishment | | | |
|--------------------------|---|------------------|----------------------|
| Name | Address | ID/FEI | Operations |
| Acme Manufacturing, Inc. | Address: 777 Sampson Street City, State, Zip: Mason, PA, 35859 Country: USA | 475859252 | manufacture |
| Contact | Address | Telephone Number | Email Address |
| Pam Jamison | Address: 777 Sampson Street City, State, Zip: Mason, PA, 35859 Country: USA | +1-800-778-8359 | pam.jamison@acme.com |

Establishment Registration

SPL Document cont...

| | | | |
|------------------------------|--|-------------------------|-----------------------------|
| | Country: FRA | | |
| Establishment | | | |
| Name | Address | ID/FEI | Operations |
| Acme International | Address: 33 Bleu Rue City, State, Zip: Paris, 20583 Country: FRA | 98583572 | manufacture, analysis |
| Contact | Address | Telephone Number | Email Address |
| Etienne St. Champs | Address: 33 Bleu Rue City, State, Zip: Paris, 20583 Country: FRA | +33-538-5859 | etienne.st-champs@acme.com |
| US Agent (ID) | Address | Telephone Number | Email Address |
| Acme USA (359582424) | | +1-800-999-5542 | jacob.goodman@acme.com |
| Importer (ID) | Address | Telephone Number | Email Address |
| Franklin Imports (252597793) | | +1-888-444-5835 | paula.johansen@franklin.com |

Revised: 09/2008

Types of Operations

- Acceptable types of operations for establishments:
 - ANALYSIS
 - MANUFACTURE
 - RECOVERY
 - RELABEL
 - REPACK
- Unacceptable types of operations for establishments:
 - IMPORT
 - UNITED STATES AGENT

*** More types of operation **terms** will be added in future

ER SPL Notes

- Include postal code for all establishments unless one does not exist.
- Entering provinces - The province, "BC", goes in the <state> tag.
- No limit to amount of importers
- No limit to number of establishments in one SPL
- Use ISO-3166 Country Code
- Use "USA" as the country code for Puerto Rico

Correcting Mistake in Valid SPL Just Submitted

- Correct a mistake in an SPL file just submitted
 - Open the SPL file, correct the mistake,
 - Use
 - **new id root**
 - **new version number**
 - **original setId root**
 - appropriate effective time.

***SPL file was **valid** and loaded into FDA eList system

Updating an ER SPL

- Update information for an **electronically** registered establishment
- Update **anytime** during year **or** for annual registration
 - Open the previous SPL file and fill in the new information **without changing the other existing information.**
 - Use
 - new id root
 - new version number
 - original setId root
 - appropriate effective time.

Adding a New Establishment

- Add a new establishment to your ER SPL file:
 - Open the previous SPL file
 - Fill in the information on a new establishment **without changing the information on the other establishments.**
 - Use
 - **new** id root
 - **new** version number
 - **original** setId root
 - appropriate effective time.

Removing an Establishment

- Remove a previously **electronically** registered establishment
 - Open the previous ER SPL file, **without changing the existing information on the other establishments**, and remove the specific establishment information.
 - Use
 - **new** id root
 - **new** version number
 - **original** setId of your ER SPL
 - appropriate effective time.

Establishment Re-Registration

No Changes

- Applicable for registrants who have **previously electronically registered** drug establishments at least once.
- Simple process for annually re-registering establishments which have no changes
- Submit No Change Notification SPL

Establishment Re-Registration

No Changes

- No changes to registration information
 - Each year when the information is updated, if there is no change:
 - Create an SPL file with the *document type* **No change notification** with a **new** id root and **new** version number with the **original** setId and the appropriate effective time.
 - Registrant and establishment information is **not** included with an SPL file with the *document type* **No change notification**.

Establishment No Change Notification SPL

| | |
|----------------------------|------------------------|
| Product Information | |
| Product Type | NO CHANGE NOTIFICATION |

Revised: 04/2008

Going Out of Business?

- Applicable for registrants who have **previously electronically registered** drug establishments at least once.
- If the registrant goes out of business, create an SPL file with the *document type* **Out of business notification** using a **new** id root and **new** version number with the **original** setId and the appropriate effective time.
- Registrant and establishment information is not included with an SPL file with the *document type* **Out of business notification**.

Establishment Out of Business Notification

| | |
|----------------------------|------------------------------|
| Product Information | |
| Product Type | OUT OF BUSINESS NOTIFICATION |

Revised: 09/2008

US Agent

- **US Agent**
 - Name
 - DUNS number
 - Telephone Number
 - Email Address

US Agent

- No more **paper** US Agent letters -
Submission of information about US Agent
replaces the paper letter
- Each foreign establishment in an ER SPL
should have a US agent

Importer

- *...under section 510(i)(1)(A) of the Act, the name of each importer that is known to the establishment (this means each U.S. company or individual in the United States that is an owner, consignee, or recipient, of the foreign establishment's drug, that is imported into the United States. An importer does not include the consumer or patient who ultimately purchases, receives, or is administered the drug, unless the foreign establishment ships the drug directly to the consumer or patient.); and the name of each person who imports or offers for import (this means the name of each agent, broker, or other entity, other than a carrier, that the foreign drug establishment uses to facilitate the import of their drug into the United States).*

(from "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing")

Importers

- **Importer (if applicable)**
 - Name
 - DUNS number
 - Telephone Number
 - Email Address
- May or may not be an importer for each foreign establishment – Foreign establishments which do not export a drug product that is not imported into the US does not need to include importer data elements.

Certified 2656 Paper Form?

- No certified paper forms for e-registered establishments
- Check DFARS website for electronically registered establishments
- FDA inspectors requesting paper 2656 form?
 - Recommend DFARS website
 - If necessary, contact your local District Director as part of the conflict prevention and resolution process.

Listing/Content of Labeling SPL

UNII Update

- Substance Registration System team is assigning UNIs as quickly as possible
- UNIs – Request missing UNIs via e-mail to spl@fda.hhs.gov
- Need to eList right away?
 - If UNIs for inactive ingredients are missing, request UNII, but leave out names of inactive ingredients in product data elements section until UNIs are assigned. Include in next eListing update

Combination Products

- Products with more than one part
- If the dosage form is “KIT”, then there must be one or more parts
- Each part has an overall quantity
- Marketing category and status included for each part and over all “kit”

- Include NDCs at each part package level, if available
- Product code of NDC for kit should not be identical to product codes in components of kit

Example of Combo Product

| RECOMBINATE | | | |
|---|------------------|-------------------------|-------------------------------------|
| antihemophilic factor, human recombinant kit | | | |
| | | | |
| Product Information | | | |
| Product Type | | HUMAN PRESCRIPTION DRUG | NDC Product Code (Source) 0944-2831 |
| | | | |
| Packaging | | | |
| # | NDC | Package Description | Multilevel Packaging |
| 1 | 0944-2831-10 | 1 KIT In 1 CARTON | None |
| | | | |
| QUANTITY OF PARTS | | | |
| Part # | Package Quantity | | Total Product Quantity |
| Part 1 | 1 VIAL, GLASS | | 10 mL |
| Part 2 | 1 VIAL, GLASS | | 10 mL |
| | | | |
| | | | |

- Note: Only first section of combo product data elements displayed above

Combination Products

Listing w/Medical Device Lead

- Document Type
 - Medical Device
- Marketing Categories & Numbers
 - Exempt device
 - Humanitarian Device Exemption
 - Premarket Application
 - Premarket Notification
 - (Include number associated with marketing category)
- Notes
 - Specific information about medical device is not included in SPL file for combo products
 - Medical devices are currently not listed in SPL format

Combination Products

Listing w/Medical Device Lead cont

- Marketing category is Exempt device, then the id extension consists of 3 letters
- Marketing category Humanitarian Device Exemption, then the id extension has a prefix “H” followed by 6 digits
- Marketing category Premarket Application, then the id extension has a prefix “P” or “BP” followed by 6 digits
- Marketing category C80442 Premarket Notification, then the id extension has a prefix “K” or “BK” followed by 6 digits

Active Pharmaceutical Ingredients
(APIs)/Bulk Ingredients

Listing APIs in SPL Format

- Listing an API
- Components of API SPL
 - Content of labeling sections
 - Container/carton label jpeg file
 - Text from principal display panel
 - Product listing data elements
 - Labeler and Establishment information
 - NDCs – amount varies due packaging “as ordered”

Listing APIs in SPL Format

- Packaging "as ordered"
- Route of administration is "not applicable"
- Dosage form is "powder"
- DMF numbers are not used as application numbers for APIs

Listing a API w/Finished Dosage Form Product

- Inclusion of the establishment for the API in the SPL file for the finished dosage form product. This electronically lists the API.
- Importation of API
 - The NDC for the finished product could be used for import purposes.

Finished Dosage Drug Listing - Establishment Information for API Manufacturers

- Establishment information for manufacturers of your **active pharmaceutical ingredient (API)** used in your products
 - **Recommendation** that this information **should** be included in your **electronic drug listing document** (SPL file)

Repackaged & Relabeled Drug Products

- Manufacturer unknown? - Use source NDC
- Include content of labeling for products which are repackaged or relabeled
- Acquire content of labeling of manufacturers from DailyMed, if available

PROPRIETARY NAME - name(s) of active ingredient(s) dosage form
Labeler

SPL Release Four Drug Listing Data Elements (Example w/Nonsolid Oral Dosage Form) - Revised Stylesheet

| | | | |
|---|---------------------------------|---------------------------|----------------------|
| PROPRIETARY NAME | | | |
| dosage form | | | |
| | | | |
| Product Information | | | |
| Product Type | HUMAN PRESCRIPTION DRUG | NDC Product Code (Source) | 0001-0001 |
| Route of Administration | ORAL | DEA Schedule | |
| | | | |
| Active Ingredient/Active Moiety | | | |
| Ingredient Name | Basis of Strength | Strength | |
| name(s) of active ingredient(s) (name of active moiety number 1 and name of active moiety number 2) | name(s) of active ingredient(s) | 50 mg | |
| | | | |
| Inactive Ingredients | | | |
| Ingredient Name | Strength | | |
| name of inactive ingredient | | | |
| | | | |
| Product Characteristics | | | |
| Color | | Score | |
| Shape | | Size | |
| Flavor | | Imprint Code | |
| Contains | | | |
| | | | |
| Packaging | | | |
| # | NDC | Package Description | Multilevel Packaging |
| 1 | 0001-0001-02 | 5 mL In 1 VIAL | None |

Labeler - Labeler

Data Relationships

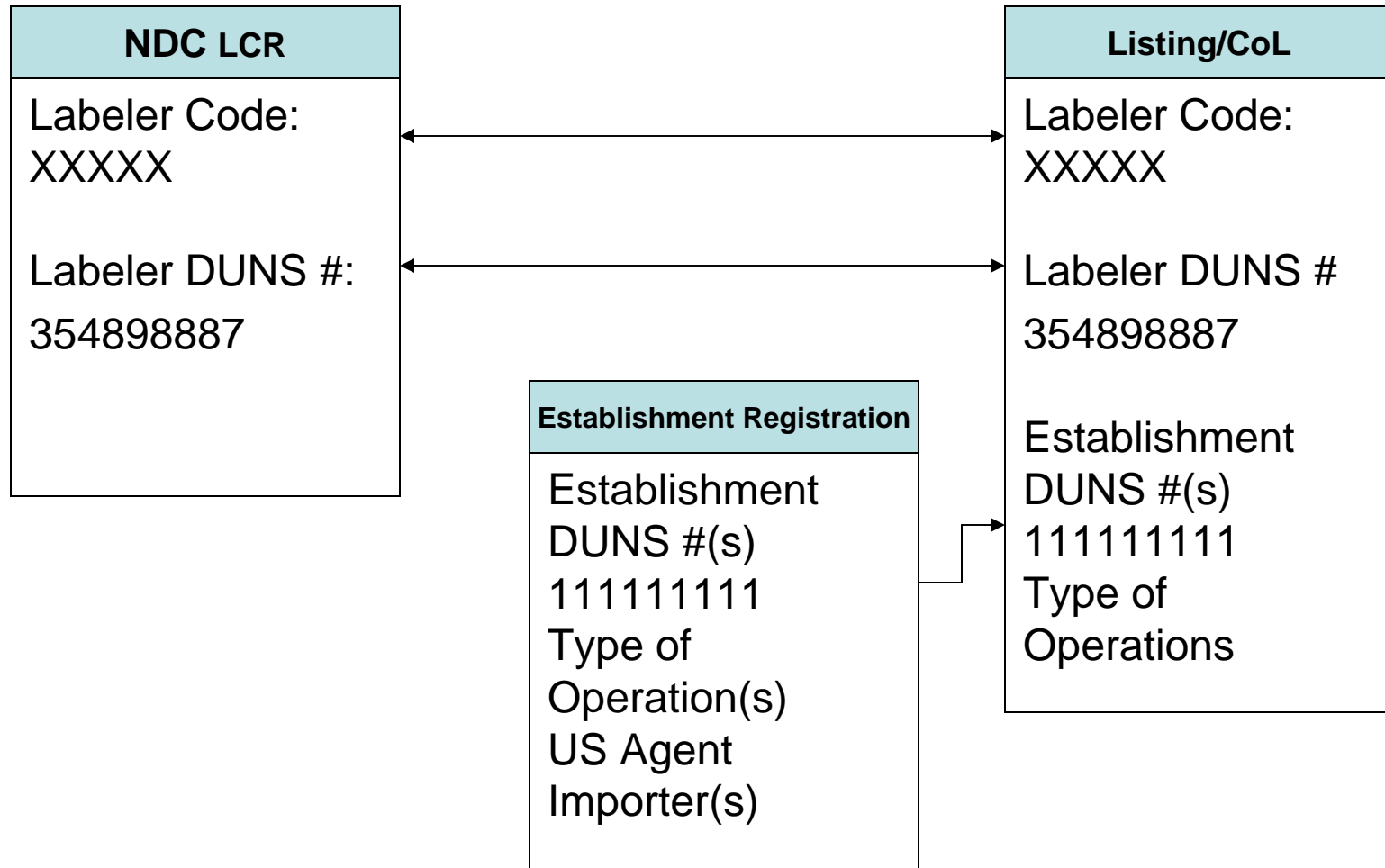
e-Files for Drug Establishment Registration & Listing – SPL Format

- NDC Labeler Code Request
- Establishment Registration
- Content of labeling (CoL)/Listing

Order of Submissions

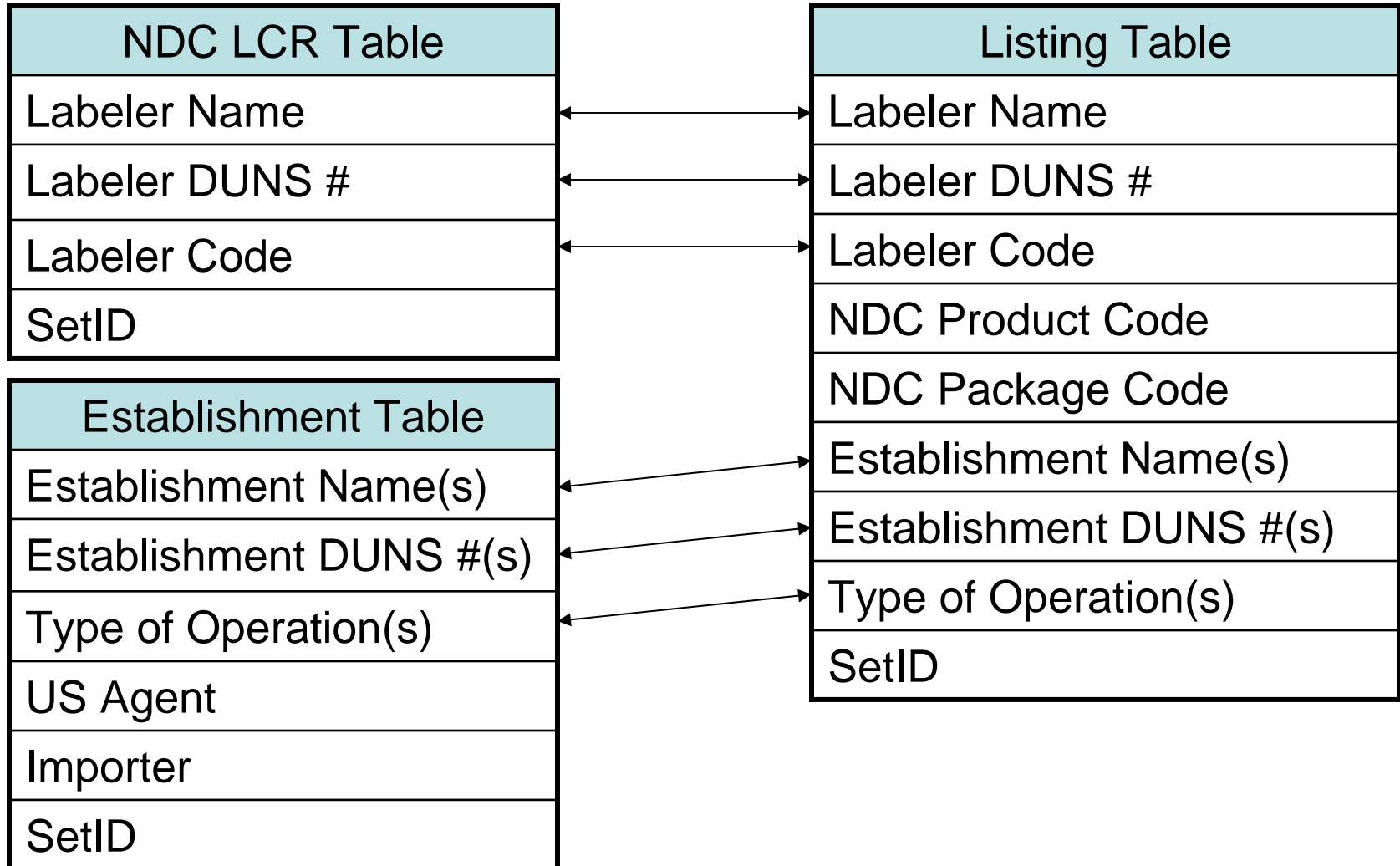
1. NDC Labeler Request (LCR) and Establishment Registration (ER) SPL
 2. CoL/Listing SPL
- CoL/Listing validates against data submitted in NDC LCR and ER SPL

Data Source – SPL Documents

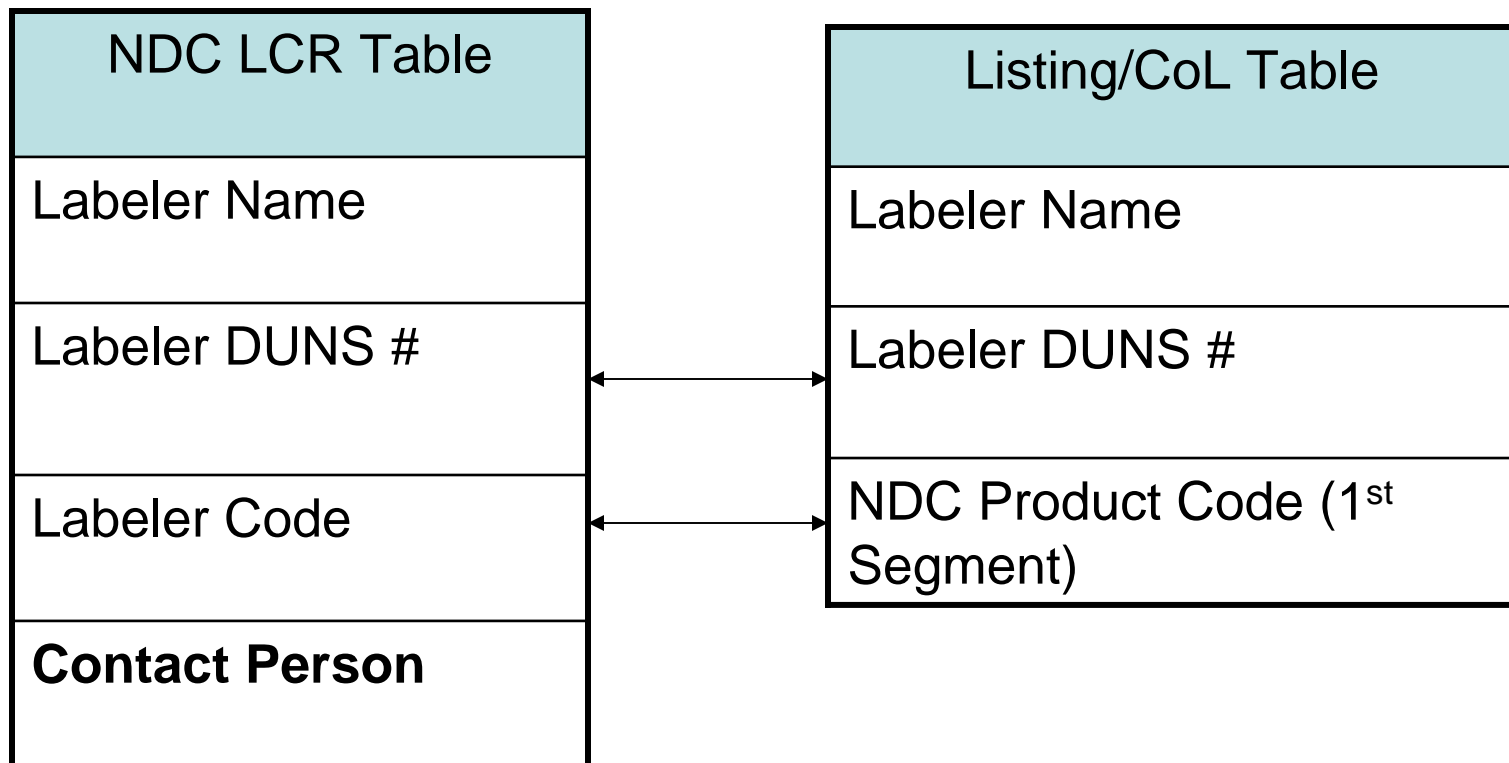


eList Data Relationships

Mockup



NDC Contact Person & Listing SPL Relationship



SPL Errors

Correcting an SPL with Validation Error

- Correct SPL file validation error
 - If an SPL file cannot be processed because of a validation error, a report on the validation error is sent from FDA to the contact person. Open the SPL file and correct the errors.
- ***SPL file **never** made it into the FDA eList system***

Correcting Mistakes in Valid SPL Just Submitted

- Correct a mistake in an SPL file just submitted
 - Open the SPL file, correct the mistake,
 - Use
 - **new id root**
 - **new version number**
 - **original setId root**
 - appropriate effective time.

***SPL file was **valid** and loaded into FDA eList system

Error Messages

- Transition (Pilot) Period
 - Error messages relayed via SPL e-mail account to contact person in NDC Labeler Code and Establishment Registration SPL files (within 24 – 72 hours average)
- Transition Period to Implementation
 - Combination of e-mail and Gateway Notification (within 24 – 72 hours average)
- Implementation
 - Gateway Notification (Check Inbox) (within 24 hours)

Error Messages cont...

- Contact FDA at spl@fda.hhs.gov regarding questions or comments regarding errors messages
- Request individual training session, if needed

Sample System Generated Validation Report

Validation Report

Document b57873cf-1ad4-4f30-bdb6-4f99baf5e46b (version 1) validated on 200-05-20 at 14:35 contained 2 errors.

Overview of Errors

1. [Value of version number must be greater than the value of any previously submitted version for the same setId](#)
2. [id must be unique across all documents](#)

XML View

Click on the XML tag to expand or collapse. The marks identified like this **2** indicate thus many errors are in the collapsed element. Errors are shown in **red comments, such as this**. Double-click to expand all.

```
<document xsi:schemaLocation="urn:hl7-org:v3 http://www.accessdata.fda.gov/spl/schema/spl.xsd" v:schemaVersion="2.0">
  <!-- Value of version number must be greater than the value of any previously submitted version for the same setId [1.3.16, go back] -->
  <id root="b57873cf-1ad4-4f30-bdb6-4f99baf5e46b">
    <!-- id must be unique across all documents [1.3.5, go back] -->
    </id>
    <code code="51726-8" codeSystem="2.16.840.1.113883.6.1" displayName="NDC LABELER CODE REQUEST"/>
    <effectiveTime value="20090520"/>
    <setId root="a41f2c3e-3b09-49d4-8aaf-3537ce86b757"/>
    <versionNumber value="1"/>
    <author ... >
    <component ... >
  </document>
```

Common Errors

- Uploading only XML file (Upload folder containing SPL (XML) file)
- Spaces preceding or following e-mail or telephone number
- Inclusion of “Thumbs.db” file
- Zipping files
- Mismatched DUNS Numbers

Test Your SPL R4 Docs

- Provision of SPL R4 Validator Tool
- Test SPL R4 files prior to submission
- Discover ~90 – 95% of validation errors prior to submission.
- Schematron technology – permits quick updates to validation procedures
- FDA in collaboration with Pragmatic Data makes available a validation tool:
[Pragmatic Validator Lite™](#)

Use These Documents

- **Use** these most recent version of these source documents when authoring your SPL:
 - FDA SPL schema
 - FDA SPL stylesheet
 - SPL Implementation Guide
 - SPL Validation Procedures
 - SPL XForms instructions document
 - Appropriate regulatory guidance documents
 - Appropriate labeling and listing regulations

*** Most SPL-related regulatory guidance and technical documents are available on FDA Data Standards Council website – SPL Labeling Resources web page <http://www.fda.gov/oc/datacouncil/spl.html>

FDA SPL R4 Training Goals

- Ensure percentage of “valid” SPL R4 submissions surpasses amount of invalid SPL R4 submissions.
- Provide as many training opportunities as are needed – individual company and group sessions
- Assist SPL R4 software vendors to ensure that they can provide great software tools

Future SPL R4 Training Sessions

- SPL Software Vendor Validation Procedures Overview – June 2009
- Session 8 - June 10, 2009, Face-to-Face – Rockville, MD, 9:30 a.m. – 3:30 p.m.
- SPL Xforms Training – June 2009
- Session 10 - June 11, 2009 - July 16, 2009, Web conferences
- Session 11 - July 23, 2009 - August 27, 2009, Web conferences
- Session 12 - September 3, 2009 - October 8, 2009, Web conferences

Pillbox – NLM Imaging Project

Product Specific SPL R4 Training Sessions

- Compressed Medical Gases – June 2009
- Over-the-Counter Drug Products – June 2009
- Bulk Drug/Active Pharmaceutical Ingredient – June 2009
- Combination Products – June 2009
- Possible Meeting Format – Face-to-Face/Web Conference Combination (for these sessions only)

Q&A

Questions

**THANK YOU
FOR
YOUR
ATTENDANCE**